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ALLERGIC PHENOMENA FOLLOWING INTRA-PORTAL INJECTIONS

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The portal blood differs from that in the general circulation in several important respects. It has been through the capillaries of the intestinal tract, and is going to the liver capillaries without aeration or contact with the tissues. During its passage through the intestinal villi it comes in contact with many cells whose function is to absorb and throw into the blood stream the various products of tryptic digestion. As I have pointed out,[1] it is probable that the proteolytic ferments are also absorbed to a certain extent and carried to the liver. It is probable, too, that the CO_2 tension in the portal blood is much greater than that in the peripheral blood because of the decreased pressure and slower circulation. This condition would tend to increase the rate of proteolysis because it has been found that under these circumstances proteolysis occurs more rapidly than when the CO_2 tension is normal.

It is not definitely known whether the protein molecules are completely broken down to the end stages of tryptic digestion before absorption or whether rather large fragments of the molecules may not be taken up as such and broken down to amino-acids by the liver before gaining entrance to the peripheral blood stream. It is well known that the liver is rich in ferments, as shown by the rapidity of autolysis post-mortem under favorable circumstances. Also its position in intimate relation to the digestive tract in its embryologic development from the archenteron indicates that it is an integral part of the ferment producing mechanism of the body. With these facts in mind, it is not unreasonable to suppose that protein substances might produce atypical reactions in the allergic sense when introduced into the portal as compared with the general circulation. This would seem the more probable since heretofore it has been assumed by Abderhalden[2] and others that the liver acts as a buffer between the intestinal tract and the general circulation, and protects the latter from the entrance of foreign protein which, when split, would be a potential source of protein poison.

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[1] Jour. Am. Med. Assn., 1915, 65, 524.

[2] Beitr. z. klin. Infektionskr. u. Immunitätsforschung, 19.

Manwaring,[3] in an attempt to locate the seat of the reaction in anaphylactic shock, came to the following conclusion:

> The acute anaphylactic shock in dogs is an explosion like autointoxication originating in the liver and digestive tract. This autointoxication is modified, restricted, and overcome by a more or less powerful antianaphylactic mechanism which has its origin in part at least in other organs. Further, the present state of our knowledge permits us to put forward working hypotheses regarding the chemical nature of the autointoxication.

Some evidence has been brought forth to show the possibility of sensitization and of producing shock phenomena through the portal system by feeding certain proteins.

Thus, La Roche, Richet and St. Girons[4] sensitized guinea-pigs by feeding cow's milk and then shocked them by intradural injections. It took 12 days for the anaphylactic state to develop; none of the pigs died.

Richet,[5] by feeding krepetin to dogs sensitized them so that death resulted with shock when intravenous injections were made that ordinarily were harmless. Also, after injecting a dose of sufficient size to be on the borderline of toxicity, toxic symptoms resulted on feeding krepetin, but in no case did death result. Vaughan[6] has shown that rabbits may be sensitized by injecting the blood of rabbits which have previously had egg-white injected into the stomach or rectum. This, he thinks, shows that the egg-albumin may be absorbed in part at least unchanged. However, this conclusion hardly follows from the experiments detailed, because the protein molecule may be split to a considerable extent (i. e. till it no longer gives a biuret reaction) and still retain its power to sensitize. Chiray[7] has studied the effects of the administration of heterologous proteins. The intravenous injection of a small amount of egg-white in rabbits causes a transitory albuminuria in 30 minutes. The albuminuria appears much later when the injection is made into the portal vein. Subcutaneous injections cause an albuminuria which appears later, is less marked, and persists longer than when intravenous injections are made. He came to the conclusion also that alimentary albuminuria in rabbits following rectal injections of egg-albumin is not due to poisons resulting from the splitting of the protein molecules, but to the absorption and elimination of the unbroken protein molecule, which is a foreign and poisonous body. He also found that casein may in some instances be found in the urine when a milk diet is given. Wells[8] found that egg-white subjected to tryptic digestion lost its sensitizing properties as the stage of digestion progressed.

It seemed of interest to study the reaction after intraportal protein injections to determine if possible whether or not animals could be sensitized by portal injections of foreign proteins, and, if sensitized by this type of injection, whether or not anaphylactic shock could be produced by the same route; further, whether an animal could be sensitized by portal injection and shocked by peripheral intravenous injection, and sensitized by peripheral and shocked by intraportal injection; also, if differences in the sensitizing and shock doses necessary to produce the reaction could be detected, when using the portal or peripheral circulation as the place of injection.

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[3] Ztschr. f. Immunitätsf. u. Exper. Therap., 1910, 8, p. 1.

[4] Compt. Rend. Soc. Biol., 1911, 70, p. 169.

[5] Ann. de l'Inst. Pasteur, Par., 1911, 15, 580.

[6] Protein Split Products, 355.

[7] Thèse de Paris, 1906, Jahresbericht d. Tierchemie, 1907, 36, p. 805.

[8] Jour. Infect. Dis., 1908, 5, p. 449.

Young guinea-pigs as nearly as possible of uniform size were selected for the reason that these animals are responsive to protein injections both as to sensitization and as to characteristic shock phenomena.

Human blood serum was used as the antigen for 2 reasons. First, because it could be easily obtained fresh; second, in order to learn more about its action as an antigen concerning which but little is found in the literature. The sensitizing dose was uniformly 0.002 c.c. of a fresh 1:100 dilution of serum in physiologic salt solution, in the cases in which the injections were made intravenously. When the sensitizing dose was given intraperitoneally this same amount was given in some cases, in others 0.005 c.c. was used. The shock doses were given intravenously in all, and were usually composed of the whole serum. They varied in size in order that the effects of varied amounts might be studied.

Injections were made with a fine needle attached by a short rubber coupling to a pipet, graduated to one-tenth c.c.; rubber tubing on the other end of the pipet allowed blowing after the needle was placed in the vein. This was an advantage since it reduced manipulation to the minimum, which is very desirable when working with such fine structures as the mesenteric veins of guinea-pigs under light ether anesthesia. A large vein was selected and a ligature of cotton thread placed around it, but not tied. The vein was punctured just below the ligature and the injection made, the amount being read off on the graduated pipet. The needle was removed and the ligature tied. Peritonitis did not develop. Peripheral intravenous injections were made in the usual way into the jugular vein.

I have grouped the animals used in these experiments into 6 groups. As a preliminary experiment 0.002 c.c. was injected intraportally into a guinea-pig. The animal died suddenly with all the appearances and findings of anaphylactic shock. This experiment was suggestive; nothing similar occurred in subsequent injections, the nearest approach to anaphylactic phenomena being a roughening of the coat and emptying of bladder and rectum when a dose of this size was given intraportally; recovery followed in all cases. With 0.005 c.c. instead of 0.002 c.c. only slight shock symptoms resulted.

Group 1.—Six pigs (3-8) received 0.002 c.c. of human serum intraperitoneally and 17 days later 0.2 c.c. of the same serum by intraportal injection. Pig 3 showed slight shock symptoms but 4 and 5 showed no effects of the injection. The other 3 pigs of this group were injected intravenously into the jugular vein with the same dose, and all showed slight shock symptoms.

Group 2.—Five pigs (9-13) sensitized intraportally with 0.002 c.c. and shocked with various doses intrajugularly with the exception of Pig 13, which received both the doses intraportally. Pigs 9, 10 and 11 received 0.5 c.c., 0.4 c.c., and 0.3 c.c. respectively; 9 and 10 died in 4 minutes, 11 died in about 5 minutes. Pig 12 received 2 c.c. peripherally and gave only slight symptoms. Pig 13, which received the shock dose as well as the sensitizing dose intraportally, showed no effect even though the shock dose of 0.5 c.c. was equal to nearly twice the minimum fatal dose necessary to kill with injection into the peripheral circulation.

Group 3.—Five pigs (14-18) were sensitized intraperitoneally with 0.005 c.c. After 17 days Pig 14 received 0.4 c.c. intrajugularly and died in 2 minutes. Pig 15 received the same dose intraportally and showed no effect. Pig 16 received 0.6 c.c. intraportally with negative result. Pig 17 received 1 c.c. intraportally and showed marked signs of anaphylaxis but recovered. Pig 18 received 1.5 c.c. intraportally and died in 20 minutes.

Group 4.—In order to test the effect of this type of sensitization and shock injection on passive anaphylaxis, 4 pigs were injected with the blood serum of Pig 19, Group 3, which had been sensitized by the intraperitoneal injection of 0.005 c.c. of human serum 16 days previously; 0.2 c.c. was the dose for passive sensitization, and Pigs 20 and 21 were sensitized passively intraperitoneally, while 22 and 23 were sensitized passively intraportally. The shock dose, administered one hour later, was uniformly 1 c.c. of whole human serum. Pig 20, sensitized passively intraperitoneally and shocked by intrajugular injection, showed marked dyspnea and itching, but recovered completely. Pig 21, sensitized passively intraperitoneally and shocked intraportally

TABLE 1

SUMMARY OF EXPERIMENTS

Group	Guinea-Pig	Sensitizing Dose in C.c.	Injection	Shock Dose in C.c.	Injection	Result
I	1	0.002	Intraportal	...	....	Died 3 min.
	2	0.005	Intraportal	...	....	Slight shock symptoms
	3	0.002	Intraperitoneal	0.2	Intraportal	Slight shock
	4	0.002	Intraperitoneal	0.2	Intraportal	No shock
	5	0.002	Intraperitoneal	0.2	Intraportal	No shock
	6	0.002	Intraperitoneal	0.2	Intrajugular	Slight shock
	7	0.002	Intraperitoneal	0.2	Intrajugular	Slight shock
	8	0.002	Intraperitoneal	0.2	Intrajugular	Slight shock
II	9	0.002	Intraportal	0.5	Intrajugular	Death 4 min.
	10	0.002	Intraportal	0.4	Intrajugular	Death 4 min.
	11	0.002	Intraportal	0.3	Intrajugular	Death 5 min.
	12	0.002	Intraportal	0.2	Intrajugular	Slight shock
	13	0.002	Intraportal	0.5	Intraportal	No effect
III	14	0.005	Intraperitoneal	0.4	Intrajugular	Death 2 min.
	15	0.005	Intraperitoneal	0.4	Intraportal	No effect
	16	0.005	Intraperitoneal	0.6	Intraportal	No effect
	17	0.005	Intraperitoneal	1.0	Intraportal	Marked reaction, recovery
	18	0.005	Intraperitoneal	1.5	Intraportal	Death 20 min.
IV	20	0.002	Intraperitoneal	1.0	Intrajugular	Marked shock, recovery
	21	0.002	Intraperitoneal	1.0	....	Slight shock
	22	0.002	Intraportal	1.0	Intrajugular	Marked shock, recovery
	23	0.002	Intraportal	1.0	....	Slight shock
V	24	0.002	Intraportal	0.4	Intrajugular	Marked reaction, recovery
	25	0.002	Intraportal	0.5	Intraportal	No effect
	26	0.002	Intraportal	1.0	Intraportal	Slight reaction
	27	0.002	Intraportal	1.5	Intraportal	Marked reaction
	28	0.005	Intraperitoneal	0.4	Intrajugular	Death 5 min.
	29	0.005	Intraperitoneal	0.5	Intraportal	Slight irritation
	30	0.005	Intraperitoneal	0.8	Intraportal	Death 20 min.
	31	0.005	Intraperitoneal	1.0	Intraportal	Death 30 min.
Controls	32	1.5	Intraportal	...	....	Appeared toxic, recovered
	33	1.5	Intraperitoneal	...	....	Death 4 min.
	34	1.15 Salt Sol.	Intraportal	...	....	No effect

with the same dose as used in Pig 20, showed only slight irritation. Pig 22, sensitized intraportally passively and shocked intrajugularly, showed marked dyspnea and itching, while Pig 23, which was sensitized passively intraportally and shocked intraportally, showed only slight itching.

Group 5.—A repetition of the experiments in Groups 1 and 2, the results being the same. Pig 24, corresponding to Pig 10, differed in that it recovered after a severe reaction while Pig 10 died. Pig 25 duplicates Pig 13, showing no reaction. Pigs 26 and 27 correspond to 17 and 18 except that the pigs were sensitized by intraportal injection and the reaction was less violent. Possibly this difference is due to a difference in the human serum used in the experiments. Pigs 28 to 31 are duplicates of 14 to 17 of Group 3. Pig 28 was killed in 5 minutes with a shock dose of 0.4 c.c. intrajugularly. A slightly larger dose injected intraportally in Pig 29 caused slight reaction. However, double the dose intraportally in Pigs 30 and 31 caused death in 20 and 30 minutes, respectively.

As control 1.5 c.c. of human serum was injected intraportally and intrajugularly into nonsensitized pigs. Pig 32, receiving the portal injection, appeared toxic but recovered. Pig 33, receiving the intrajugular injection, died in 4 minutes. Pig 34 received 1.5 c.c. of normal salt solution intraportally with no effect.

Necropsy was made of every pig that died, and in all cases the typical picture of acute anaphylactic shock was found—the lungs were distended, and there were subserous hemorrhages and congestion of the kidneys.

The results show that guinea-pigs may be sensitized and shocked by injections into the portal circulation. Larger doses, however, are necessary to produce the typical anaphylactic reaction than when the injections are made into the peripheral circulation. Apparently there is a protective action against foreign protein somewhere in the portal system, whether it be in the portal blood itself or whether it is a function of the liver cells. Since the shock dose must be larger to produce the same results several possibilities present themselves. First, the ferment content of the portal blood may be such that protein is rapidly split beyond the toxic stage, and hence toxic substances are not present in sufficient amount at any one time to produce the characteristic reaction. Secondly, the products of the protein molecule may unite with other products of tryptic digestion, thus masking their toxic action. Thirdly, the liver cells may unite with and detoxicate the products, thus protecting the body from their deleterious effects. Fourthly, the sluggishness of the portal circulation with normally active proteolytic digestion of the protein introduced may result in the protein toxic radicals being split beyond the toxic stage before they come in contact with the general circulation, the response to which is the characteristic phenomena of anaphylactic shock. Finally, a certain amount of the injected protein may be absorbed or bound by the liver cells before splitting occurs, leaving thus only a portion available for digestion and formation of anaphylatoxin.

The possible influence of an increased CO_2 tension causing an increased proteolysis due to stimulation of the catalytic action of the ferments by increasing the H-ion content of the blood is suggested by the interesting work of Bradley on intracellular ferment activity.

CONCLUSIONS

Guinea-pigs may be sensitized by intraportal injections of human serum.

Anaphylactic shock may be evoked after the usual latent period by subsequent intraportal injection.

Guinea-pigs may be sensitized by intraportal injections and shocked by peripheral intravenous injections of human serum.

Conversely, guinea-pigs may be sensitized by intraperitoneal injections and shocked by intraportal injections.

Larger doses are necessary to produce anaphylactic shock in guinea-pigs when the shock dose is administered intraportally, irrespective of the method of administration of the sensitizing dose.

Passive anaphylaxis may be transmitted to guinea-pigs by way of the portal system and shock may be produced by portal or peripheral injections. Here again, however, larger doses seem necessary to produce shock when administered by the portal system.

Human serum sensitizes and produces anaphylactic shock in the guinea-pig. It is, however, not without toxic effect on nonsensitized guinea-pigs as shown by the fact that 1.5 c.c. intrajugularly caused death in 4 minutes with symptoms of anaphylactic shock, the same amount introduced intraportally producing toxic symptoms but not death.